PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
FRANK B. DEHN & CO.
Attn. COCKBAIN,DR JULIAN
179 Queen Victoria Street
GB - London EC4V 4EL
UNITED KINGDOM

FILE 70151/002
21 AUG 2000

Date of mailing (day/month/year)	22/08/2000
Applicant's or agent's file reference 44.70151/002	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB 00/01963	International filing date (day/month/year) 22/05/2000
Applicant NYCOMED IMAGING AS	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marie-Françoise Provot

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international apppllcation is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, Julian
FRANK B. DEHN & CO.
179 Queen Victoria Street
GB - London EC4V 4EL
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	30.08.2001
Applicant's or agent's file reference 44.70151/002	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01963	22/05/2000	21/05/1999

Applicant
NYCOMED IMAGING AS

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Cardenas, C Tel.+31 70 340-3370

Form PCT/IPEA/416 (July 1992)

PA NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 January 2001 (29.01.01)	
International application No. PCT/GB00/01963	**Applicant's or agent's file reference** 44.70151/002
International filing date (day/month/year) 22 May 2000 (22.05.00)	**Priority date** (day/month/year) 21 May 1999 (21.05.99)
Applicant BRILEY-SÆBO, Karen et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

19 December 2000 (19.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/72032 A1

(54) Title: METHOD OF MAGNETIC RESONANCE IMAGING

(57) Abstract: A method of interventional or intraoperative MRI wherein an invasive device is inserted into the vasculature of a human or non human animal (e.g. mammalian, avian or reptilian) body or through vascularised tissue in said body and an MR image f at least a part of said body containing said device is generated, the improvement comprising administering a contrast agent into the vasculature of said body either by direct injection f the contrast agent through said device or by i.v. injection of the contrast agent directly into the patient whereby to facilitate visualisation of said device in said image.

Method of Magnetic Resonance Imaging

The invention relates to improvements in and relating to magnetic resonance imaging (MRI), in particular to generation of magnetic resonance images of invasive devices, e.g. during surgical procedures.

During surgical and therapeutic procedures it is frequently desirable for the physician to be able to locate or guide invasive devices inserted into the body (for example catheters, guide wires, biopsy needles, etc.) when these are not directly visible to the naked eye.

Due to the reduced invasiveness of surgical procedures, MRI-guided interventional procedures have gained increasing importance in recent years. Such MRI guided procedures can be divided into two categories: intraoperative procedures which integrate surgery with MRI and interventional procedures for guiding, monitoring and controlling therapy.

Intraoperative procedures generally require an open magnet MR imager and are desirable as the MRI can be used to define anatomy and monitor tissue function as it changes during surgery. By monitoring anatomy and function in this way, the clinical outcome for the patient may be improved since complications may be reduced by reducing the degree of invasiveness of the surgery.

Interventional procedures generally require only limited patient access and thus conventional closed magnet MR imagers may be used. The high spatial and temporal resolution available in MRI allows for accurate "near real time" guidance of devices such as catheters, guide wires, biopsy needles, etc.

The success of an MRI-guided interventional or intraoperative procedure generally depends on the ability of the MRI technique to provide sufficiently accurate visualisation of the instruments and devices

inserted into the patient's body. Currently, either active or passive visualisation techniques have been used for monitoring and visualising such instruments and devices (herein generally referred to as "invasive devices").

In active visualisation, the invasive device is provided with a small signal receiving antenna (e.g. on the tip of the device). The magnetic resonance signal from water protons in the vicinity of the antenna is detected by the antenna and incorporated into the MR image generated by the MR imager. The result is a "road map" showing the movement of the antenna (and hence the device) within the patient. There are however two problems associated with active visualisation. Firstly, heat generated within the antenna may be large if large magnetic field gradients or rapid gradient switching are used in the MRI procedure. Secondly, since the signal from the device is superimposed over the original MR image, any tissue movement may result in loss in accuracy of spatial information regarding device location.

The term "passive visualisation" is used to describe the case where device visualisation relies on a difference in magnetic susceptibility between the material from which the device is made and the surrounding biological tissue or fluid. In order to increase this susceptibility difference, it has been conventional to mark the device with a magnetic (i.e. paramagnetic, ferrimagnetic, ferromagnetic or superparamagnetic) material, such as for example dysprosium oxide (Dy_2O_3). To avoid extensive marking resulting in blurring artefacts in the MR images, it has been common to incorporate small bands or rings of Dy_2O_3 or of a material containing for example 10% w/w Dy_2O_3. *In vitro* studies have shown that such Dy_2O_3-marked devices can be visualised accurately in "near real time" imaging procedures without causing significant image

artefacts (such as for example blurring or distortion) as long as the device is parallel to the primary magnetic field of the MR imager. Where the device is perpendicular to the primary field however, blurring and distortion artefacts occur which result in over-estimation of device size and decrease in spatial resolution.

Biopsy needles are currently monitored using passive visualisation; however the needles currently used produce severe image artefacts which distort the observed size and location of the needles. To compensate for this, two techniques have been developed. Firstly a laser guidance system may be used to guide the needle to the target tissue; however, using this technique, it is still difficult to determine needle depth within the tissue. Accordingly, needles have been produced which have a small inner bore at the needle tip. This is filled with a gadolinium chelate solution (e.g. a solution of Gd DTPA, Gd DTPA-bismethylamide or Gd HP-DO3A) which allows for visualisation of the needle tip in the MR image. However the gadolinium chelates used distribute rapidly into the extracellular space and thus even with single or multiple injections of the gadolinium chelate solution only temporary assistance in passive visualisation of the needle tip is achieved.

The present invention is directed to facilitating passive visualisation of invasive devices and relies instead on introducing into the vasculature a blood pool MR agent, i.e. an MR contrast agent which does not distribute into the extracellular space but instead remains substantially in the intravascular space during the time course of the visualisation procedure. The effect of the contrast agent is to enhance the relaxation properties of the blood (i.e. to reduce T_1 and/or T_2* for blood) relative to those of the invasive device. Thus, using the invention, the invasive devices traditionally utilised in intraoperative and

interventional MRI can be used.

Thus viewed from one aspect the invention provides a method of interventional or intraoperative MRI wherein an invasive device is inserted into the vasculature of a human or non human animal (e.g. mammalian, avian or reptilian) body or through vascularised tissue in said body and an MR image of at least a part of said body containing said device is generated, the improvement comprising administering into the vasculature of said body by either direct injection of the contrast agent through said device or by i.v. injection of the contrast agent directly into the patient whereby to facilitate visualisation of said device in said image.

Viewed from a further aspect the invention provides the use of a blood pool MR contrast agent for the manufacture of a parenterally administrable MR contrast medium for use in a method of surgery or therapy wherein an invasive device is inserted into the vasculature of a human or non human animal (e.g. mammalian, avian or reptilian) body or through vascularised tissue in said body and an MR image of at least a part of said body containing said device is generated, said method also comprising administering said contrast medium into the vasculature of said body whereby to facilitate visualisation of said device in said image.

By a blood pool MR contrast agent is meant a magnetic (e.g. paramagnetic, ferromagnetic, ferrimagnetic or superparamagnetic) material capable of reducing the T_1 and/or T_2* of water protons and which if administered into the vascular space does not significantly leak out into the interstitium during the time course of the interventional or intraoperative procedure, i.e. it is essentially confined to the vascular space until excreted or metabolized. Examples of such blood pool agents include polymeric chelates (e.g. cascade polymers or dendrimers carrying metallated chelate groups) and particulates, in particular iron

oxides and liposomes. Generally the agent should have a blood half life of at least 5 minutes, preferably at least 30 minutes. By way of contrast, the first parenteral MR contrast agents Gd DTPA (Magnevist® from Schering), Gd DTPA-bismethylamide (Omniscan® from Nycomed Amersham) and Gd HP-D03A (ProHance®) are all extracellular fluid MR agents; they are water-soluble mono-chelates which following administration into the vasculature rapidly extravasate into the interstitium.

Blood pool agents of particular use in the method of this invention include low molecular weight chelates which bind to blood proteins, e.g. blood proteins such as albumin, for example DTPA or DOTA derivatised with protein binding groups, e.g. lipophilic side chains such as aromatic moieties, e.g. one or more phenyl ring systems. One such example is MS-325/Angiomark of EPIX.

Suitable polymer based contrast agents for use in the method of the present invention can be carbohydrate or protein based, e.g. CMD-DTPA-Gd of Guerbet (Carboxymethyl dextran-GdDTPA conjugates), GdDTPA polylysine conjugates, or cascade or dendrimer polymers, e.g. Gadomer 17 of Schering AG or similar cascade polymers as described in US-A-5874061 (of Schering AG), herein incorporated by reference.

Suitable iron oxide (or doped iron oxide) based contrast agents for use in the method of the present invention are known in the field under the name of SPIO (superparamagnetic iron oxides) or USPIO (ultrasmall superparamagnetic iron oxides). Examples include carbohydrate stabilised iron oxide particles, e.g. dextran-stabilised particles such as Combidex of Advanced Magnetics, and NC100150 (Clariscan, Nycomed Amersham).

More particularly the magnetic iron oxide contrast agent is preferably a water-dispersible material comprising magnetic iron oxide particles having on their surfaces (e.g. as a coating), an optionally modified

carbohydrate or polysaccharide or derivative thereof, e.g. a glucose unit containing optionally modified polysaccharide or derivative thereof, preferably an optionally modified dextran or starch or derivative thereof, for example a cleaved (e.g. oxidatively cleaved) starch or carboxylated dextran. Such iron oxide complexes preferably also comprise a further material (e.g. coating material), especially one which inhibits opsonization, e.g. a hydrophilic polymer, preferably a functionalized polyalkylene oxide, more preferably a functionalized polyethylene glycol (PEG), in particular methoxy PEG phosphate (MPP).

The iron oxide complexes preferably have a core (i.e. iron oxide particle) diameter (mode diameter) of 1 to 15 nm, more preferably 2-10 nm, especially 3-7 nm, a total diameter (mode particle size) of 1 to 100 nm, more preferably 5-50 nm, especially preferably 10-25 nm, an r_2/r_1 ratio at 0.47T and 40°C of less than 3, more preferably less than 2.3, still more preferably less than 2.0, especially preferably less than 1.8. The saturation magnetization (Msat) at 1T is preferably 10 to 100 emu/gFe, more preferably 30-90 emu/gFe.

Other particulate based systems of use in the method of the present invention include liposomal or emulsion based agents.

Furthermore, compound 7228 of Advanced Magnetics can be used in the method of the present invention, as can the materials described in WO 91/12025, WO 90/01899, WO 88/00060, WO 91/12526 and WO 95/05669, all to Advanced Magnetics, and those described in WO92/11037 and WO90/01295, all of which publications are incorporated herein by reference.

Using blood pool MR contrast agents which remain in the vascular space during the MRI-guided procedure allows for extensive monitoring of the invasive device during the procedure. The method of the invention, an "induced passive visualisation" technique, not only

allows visualisation of static devices, such as stents, but also can be used to guide placement of devices, e.g. it can be used in ablation therapy to mark vessels and/or aid in the placement of the ablation device.

Currently, three types of ablation procedures are in use clinically: interstitial laser-induced thermotherapy (LITT); focussed ultrasound; and rf-ablation.

LITT is used for the destruction of local tumors in solid organs - laser light is delivered to the tumor through optical fibres and tumor destruction occurs by direct heating by the laser light. The optical fibre is introduced in MRI-guided procedures using an MRI-guided catheter; induced passive visualisation according to the invention will allow accurate visualisation of the catheter and ensure correct placement of the optical fibre tip.

During MRI-guided focussed ultrasound ablation therapy, an ultrasound transducer is moved hydraulically across the patient and the depth and position of the ultrasound focus are determined by laser optical fibres which are locked onto target from an MR image. Induced passive visualisation according to the invention will assist by increasing the accuracy of the focus positioning since the technique allows for monitoring of all major vessels surrounding the tumor, as well as of the tumor itself, throughout the procedure.

In rf-ablation therapy, a radiofrequency electrode is placed in tissue which has previously been injected with saline. The tissue around the electrode is then heated by applying 1500-1600 mA to the electrode. The technique is relatively non-specific since treatment regions vary in shape and are dependent on local saline concentration; induced passive visualisation according to the invention will increase specificity by allowing more accurate placement of the electrode and more accurate estimation of saline concentration. Again,

both tumor and surrounding vessels may be monitored throughout the procedure.

During all intraoperative and interventional procedures, complications due to bleeding increase the risks associated with the procedures. Induced passive visualisation according to the invention however allows for accurate monitoring and assessment of bleeding during the procedure. Since the blood pool MR contrast agent remains in the blood during the procedure, any damage to blood vessels that causes changes in vessel permeability can be observed.

The invasive devices which can be monitored according to the invention include, but are not limited to, catheters, balloons, optical fibres, guide wires, needles (e.g. biopsy needles), electrodes, electrode leads, implants, stents and stent graphs. Generally these devices will be diamagnetic and exhibit long T_1 values. If desired, the devices may be marked with a magnetic susceptibility agent, e.g. bands or strips containing dysprosium oxide - however such marking is not necessary and desirably is avoided. As in all MRI-guided procedures however the devices used are preferably not substantially ferromagnetic or ferrimagnetic as this will cause image defects and gradient switching may cause unwanted motion of the devices.

The MR imaging procedure used in the method of the invention may for example be any conventional MRI procedure, e.g. T_1 or T_2* weighted spin echo or gradient echo sequences. However, fast imaging procedures, such as gradient echo and echo planar imaging procedures are preferred. In a particularly preferred embodiment of the method of the invention, the imaging procedure involves administration of an iron oxide blood pool MR contrast agent, gradient echo imaging using small flip angles (e.g. 10 to 45°) and short echo times (e.g. 0.5 to 5 ms) and using larger flip angles (e.g 55 to 75°)

and longer echo times (e.g. 6 to 20 ms). In the larger flip angle/longer echo time images the signal from the contrast agent containing blood is diminished and, using both images, visualisation of the invasive device may be facilitated (especially where the device contains a gadolinium chelate solution as a marker).

Viewed from another aspect the invention provides a method of interventional or intraoperative MRI wherein an invasive device is inserted into the vasculature of a human or non human animal body or through vascularised tissue in said body and an MR image of at least a part of said body containing said device is generated, the improvement comprising administering into said body a contrast agent which remains in the vasculature during the time course of said method so that the difference in T_1 and/or T_2 and/or T_2* between the blood and said device containing a paramagnetic or diamagnetic material may be utilized to generate image contrast between blood and said device.

By containing it is meant that the device may contain the paramagnetic or diagnostic material when it is inserted or that the material may be placed in the device following its insertion.

Thus the method may involve administering a blood pool contrast agent (e.g. an USPIO) into the vasculature and filling an invasive device (before or after its insertion) with a paramagnetic agent (e.g. a gadolinium chelate) and then generating an image of the vasculature using very fast, heavily T_1-weighted sequences. In this way slice position matching with the device is unnecessary. The selectivity of differentiation between blood and device is achieved by a minor increase in echo time that would not normally result in the sequence being termed non-T_1-weighted.

Viewed from a further aspect the invention also provides methods of interventional or intraoperative MRI wherein an invasive device is inserted into the

vasculature of a human or non human animal (e.g. mammalian, avian or reptilian) body or through vascularised tissue in said body and an MR image of at least a part of said body containing said device is generated, the improvement comprising administering into said body a contrast agent which remains in the vasculature during the time course of said method so that the T_1 and/or T_2* of the blood is enhanced relative to that of said device, and wherein when enhancing the T_1 of the blood relative to said device, T_1-weighted sequences should be used and said device should be filled with diamagnetic material (e.g. saline or medication) so that the blood appears bright relative to said device, and wherein when enhancing the T_2* of the blood relative to the device, T_2 or T_2*-weighted sequences should be used and the device coated with or filled with paramagnetic material (e.g. Gd complex or Mn complex) so that said device appears bright relative to the blood.

By initially or subsequently containing it is meant that the device may contain the paramagnetic chelate (preferably a water-soluble Gd or Mn monochelate) when it is inserted or that the chelate may be filled into the device following insertion.

In both the methods of the invention it is desirable to use as the blood pool MR contrast agent a superparamagnetic iron oxide, optionally coated with an opsonization inhibitor such as PEG, e.g. as described in WO97/25073. Such particles allow T_1 effects to predominate in heavily T_1-weighted imaging sequences - leading to an increased signal intensity for blood relative to invasive device (i.e. a "bright blood" technique) - and allow T_2* effects to predominate when T_2-weighted imaging sequences are used - leading to a decreased signal intensity for blood relative to invasive device (i.e. a "black blood" technique). Such black blood techniques are used where paramagnetic

devices or devices with paramagnetic markers are used. The bright blood technique is used with diamagnetic devices which contain a diamagnetic material (e.g. saline or medication).

The dosage of the contrast agent used according to the invention will depend upon the species, the longitudinal relaxivity of the agent, the magnetic moment of the agent at the imaging field strength and the sequence parameters used to acquire the image. Desirably the blood pool MR contrast agent is administered at dosages sufficient to achieve T_1 values in blood, at steady state, of less than 300 ms, more preferably less than 200 ms and still more preferably less than 100 ms.

In MR procedures in which a blood pool contrast agent is to be administered into the vasculature, this would normally be done outside the region of interest for imaging, e.g. in a peripheral vein and one would not expect images of the catheter to be generated either on contrast agent administration or on contrast agent circulation (or recirculation) past the catheter. Thus in the methods of the invention the invasive device may be a catheter used for administration of the blood pool contrast agent; however more generally and preferably the invasive device will be other than a device through which the blood pool contrast agent is administered.

The blood pool contrast agent will preferably be administered by injection or infusion into the vasculature, for example infused over periods of 2 seconds to 5 minutes.

The contrast agent will desirably be formulated in a sterile aqueous medium, optionally containing further excipients such as pH modifiers, osmolality modifiers, chelating agents, etc.

The methods of the invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings, in which:

Figure 1 shows the construction of two phantoms use to study the feasibility of catheter tracking by MRI;

Figure 2 shows a bright blood image of phantoms having catheters filled with saline (top) or 10mM Omniscan (bottom) and placed perpendicular to the applied field;

Figure 3 shows a bright blood image of phantoms having catheters filled with saline (left) or 10mM Omniscan (right) and placed parallel to the applied field;

Figure 4 shows a dark blood image of a phantom having a catheter filled with 10 mM Omniscan and placed perpendicular to the applied field;

Figure 5 shows a summary of an MRI signal optimisation study conducted at TR/TE=5.0/1.5 ms (Fig 5a) and TR/TE=18.0/9.0 ms (Fig 5b) with varying flip angles and concentrations;

Figure 6 shows spoiled GRE images of phantoms collected with parameters TR/TE/FA=5.2/1.2/40° (Fig 6a) and TR/TE/FA=18/9.0/70° (Fig 6b); and;

Figure 7 shows spoiled GRE *in vivo* images of the abdomen of a pig collected with parameters TR/TE/FA=5.2/1.2/40° (Fig 7a) and TR/TE/FA=18/9.0/70° (Fig 7b).

An aqueous suspension superparamagnetic iron oxide MR contrast agent, prepared according to the description of Example 12 of WO 97/25073 was used in these Examples.

The characteristics of the suspension were as follows:

[Fe] = 30.2 mg Fe/ml, density = 1.0589 g/ml, r_1 = 19.3 $s^{-1}mM^{-1}$, r_2 = 31.2 $s^{-1}mM^{-1}$, r_2/r_1 = 1.61, saturation magnetisation (Msat) = 84 emu/g Fe.

Example 1

Phantom Study

A simple *ex vivo* phantom study was performed in order to assess the feasibility of performing induced passive catheter tracking by reducing T_1 and T_2* of blood. Two phantoms were prepared by placing sections of a conventional interventional catheter (Pebax Souple 5F with inner diameter of 1.17 mm and outer diameter of 1.69 mm) into two plastic tubes of 10 mm diameter and 85 mm length inside 21 mm diameter, 60 mm length glass vials. The plastic tubes were fixed in the vial in a 2% agar gel containing gadolinium polymers (e.g. a gadolinium polychelate such as polylysinepolyDTPA.Gd) so that the T_1 of the gel at 40°C was 535 ms. The plastic tubes were filled with fresh human blood (Hct = 47%) containing sodium heparin. The iron oxide contrast medium was added to the blood so that the concentration of Fe added was 1.0 mM Fe (which is equivalent to a dose of 4 mg Fe/Kg bodyweight). One of the catheters was then filled with saline and sealed and the other catheter was filled with 10 mM Omniscan® (10 mM Gd DTPA-bismethylamide) and sealed. The arrangement was as shown in Figure 1 of the accompanying drawings. All imaging was performed at 1.5 T (Philips Gyroscan ACS-NT) using T_1 and T_2-weighted 3D-gradient echo sequences (FFE). Table 1 shows the sequence parameters which were kept constant for all experiments.

Table 1: Pulse Sequence parameters for static *in vivo* phantom imaging

Parameter	Value
TR	15.4 ms
Slice thickness	0.7 mm
Field of view	140 x 140
Nmat	256 x 256
NEX	2
Flip angle	30°

The following two imaging series were performed on the phantoms:

Series 1: Phantoms placed perpendicular relative to the applied field. Images were acquired at echo times (TE) of 2 ms (for bright blood) and 12 ms (for black blood).

The phantoms were removed from the magnet and inverted several times to ensure the homogeneity of the blood samples prior to the on set of imaging Series 2.

Series 2: Phantoms placed parallel relative to the applied magnetic field. Images were acquired using a TE of 2 ms so that bright blood was obtained.

Figures 2, 3 and 4 of the accompanying drawings show the results obtained when either the T_1 (bright blood obtained using short echo times) or T_2* (dark blood obtained using long echo times) of the blood is reduced relative to the device. In Figures 2 and 4 the phantoms were placed perpendicular relative to the applied magnetic field and Figure 3 shows the phantom placed parallel relative to the applied field. In Figures 2 and 3, short echo times were used so that the T_1 of the blood was reduced relative to that of the catheters. Figure 2 shows the phantoms placed perpendicular to the applied field. The catheters were filled with either

saline (top) and 10 mM Gd DTPA-BMA (bottom). In Figure 3, the phantoms were placed parallel to the applied magnetic field and the catheter containing the saline is shown to the left and the catheter containing the Gd DTPA-BMA is shown to the right. The diameter shown in these figures represents the total catheter diameter estimated by MRI. The actual catheter diameter for all phantoms was 1.69 mm.

The catheter filled with saline represents a conventional interventional catheter. The catheter filled with 10 mM Omniscan® represents an MRI catheter containing a paramagnetic tracer. The results clearly indicate the size of the catheter (total diameter) was underestimated when the catheter was filled with 10 mM Omniscan®. However, when the catheters were filled with saline (which represents a normal interventional procedure) fairly accurate estimates of size were obtained. The under-estimation of size observed when using a paramagnetic tracer is most likely due to the fact that the wall of the catheter has very few protons and consequently is not MR-visible. This means that the signal coming from the outer wall of the catheter is dark relative to the signal inside the catheter (which contains 10 mM Gd) and signal of the blood (which contains the iron oxide contrast medium). As a result, the size reflects only the inner-diameter of the catheter. However, when saline is used, a homogeneous dark signal is observed which accurately reflects catheter size. This is due to the fact that the catheter and the saline filling the catheter both appear hypointense relative to the blood containing the iron oxide contrast medium (bright blood obtained using short echo times).

No artefacts were observed for either phantom in any orientation relative to the applied field.

Figure 4 shows the results obtained when the T_2* of the blood is reduced relative to that of the device by

increasing the echo times used. Here the blood appears black since the reduction of T_2* dominates the observed signal. For "black blood", only the catheter filled with 10 mM Gd (representing the paramagnetic tracer catheter) is visible. The diameter shown represents the diameter estimated by MRI. The actual diameter was 1.69 mm. The phantom was placed perpendicular relative to the main field. The size of the catheter obtained by MR still reflects only the inner-diameter.

Example 2

Example 2 summarises a study performed in order to determine the optimal imaging sequence parameters required for passive induced visualisation when black blood techniques are employed (catheter filled with a paramagnetic tracer, blood containing the iron oxide contrast medium and long echo times used to enhance the T_2* of the blood relative to the catheter).

Figures 5A (TR/TE=5.0/1.5 ms) and 5B (TR/TE=18.0/9.0 ms) show experimental signal-intensity profiles of diluted Gd solutions as a function of concentration and flip angle. Brighter zones correspond to higher signal intensity. Note the shift of the signal maximum towards lower concentrations for longer echo times.

A catheter (0.8 mm inner diameter) with an Omniscan®/H_2O (0.01 M) filled guide-wire lumen was inserted into a flexible tube (i.d. 5 mm) filled with the iron oxide contrast medium (0.5 mg Fe/ml). Spoiled 2D and 3D GRE images (2D imaging without slice selection) were collected with two different echo times (NEX=1, 256x192x20, FOV=28x14 cm) as shown in Figures 6A (3D TR/TE/FA=5.2/1.2/40°) and 6B (2D TR/TE/FA=18/9/70°).

Example 3

In this example the black blood technique was used

in vivo by accessing the right femoral artery of two pigs under general anaesthesia. For display of the vascular system the iron oxide contrast medium was administered intravenously at a dose of 5 mg Fe/kg bodyweight. Via the femoral approach, a 5F PTA catheter was introduced into the abdominal aorta. The 40x12 mm balloon was filled with a 7.7 mM Gd solution of GdDTPA-bismethyl-amide and imaged with spoiled GRE sequences. The experiment was repeated with a 6F catheter in which the guide-wire lumen was filled with the Gd-solution. Figures 7A (3D TR/TE/FA=5.2/1.2/40°) and 7B (2D TR/TE/FA=18/9/70°) show the resulting spoiled GRE *in vivo* images of the abdomen of the pig. Note the bright signal intensity of both vascular system and catheter balloon in the short-echo image. With TE=9 ms only the balloon (arrow) and blood in the intraperitoneal cavity from a preceding experiment remain visible.

Claims

1. A method of interventional or intraoperative MRI wherein an invasive device is inserted into the vasculature of a human or non human animal (e.g. mammalian, avian or reptilian) body or through vascularised tissue in said body and an MR image of at least a part of said body containing said device is generated, the improvement comprising administering a contrast agent into the vasculature of said body either by direct injection of the contrast agent through said device or by i.v. injection of the contrast agent directly into the patient whereby to facilitate visualisation of said device in said image.

2. A method of claim 1 wherein said contrast agent is a blood pool contrast agent.

3. A method as claimed in claims 1 or claim 2 wherein the difference in at least one parameter chosen from T_1, T_2 and T_2* between the blood and said device is utilised to generate image contrast between the blood and said device.

4. A method as claimed in any of claims 1 to 3 wherein said device is filled with a diamagnetic material or a paramagnetic material.

5. A method as claimed in any of claims 1 to 4 wherein said contrast agent enhances the T_1 and/or T_2* relaxation properties of the blood relative to that of said device.

6. A method as claimed in claim 5 wherein the T_1 relaxation property of the blood is enhanced relative to that of said device and wherein T_1-weighted sequences are used and said device filled with diamagnetic material so that the blood appears bright in said image, relative to said device.

7. A method as claimed in claim 5 wherein the T_2* relaxation property of the blood is enhanced relative to that of said device and wherein T_2*-weighted sequences are used and said device filled with paramagnetic material so that said device appears bright in said image, relative to the blood.

8. A method as claimed in any of claims 1 to 7 wherein said contrast agent is magnetic iron oxide blood pool contrast agent.

9. A method as claimed in any of claims 1 to 8 wherein said contrast agent comprises superparamagnetic iron oxide particles having on their surfaces degraded starch and optionally a material which inhibits opsonization.

10. A method as claimed in any of claims 1 to 9 wherein said device is chosen from catheters, balloons, optical fibres, guide wires, needles, biopsy needles, electrodes, electrode leads, implants, stents and stent grafts.

11. A method as claimed in any of claims 1 to 10 wherein said device is not marked with a magnetic susceptibility agent.

12. The use of a blood pool MR contrast agent for the manufacture of a parenterally administrable MR contrast medium for use in a method of surgery or therapy wherein an invasive device is inserted into the vasculature of a human or non human animal body or through vascularised tissue in said body and an MR image of at least a part of said body containing said device is generated, said method also comprising administering said contrast medium into the vasculature of said body whereby to facilitate visualisation of said device in said image.

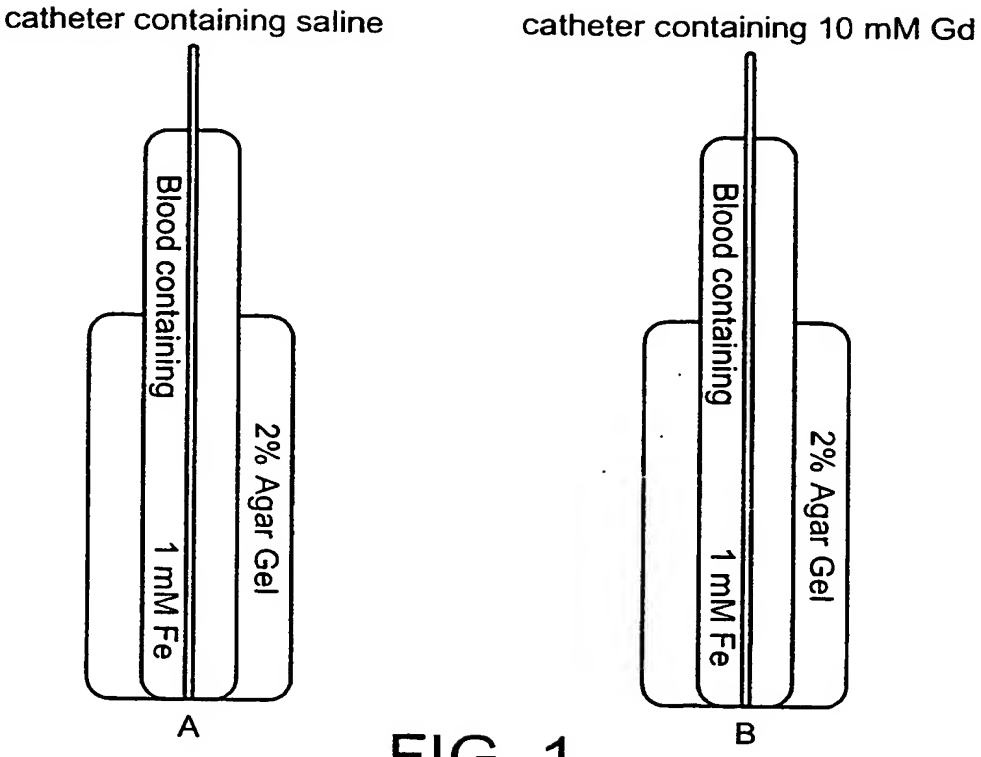
catheter containing saline
Blood containing
1 mM Fe
2% Agar Gel
A
catheter containing 10 mM Gd
Blood containing
1 mM Fe
2% Agar Gel
B

FIG. 1

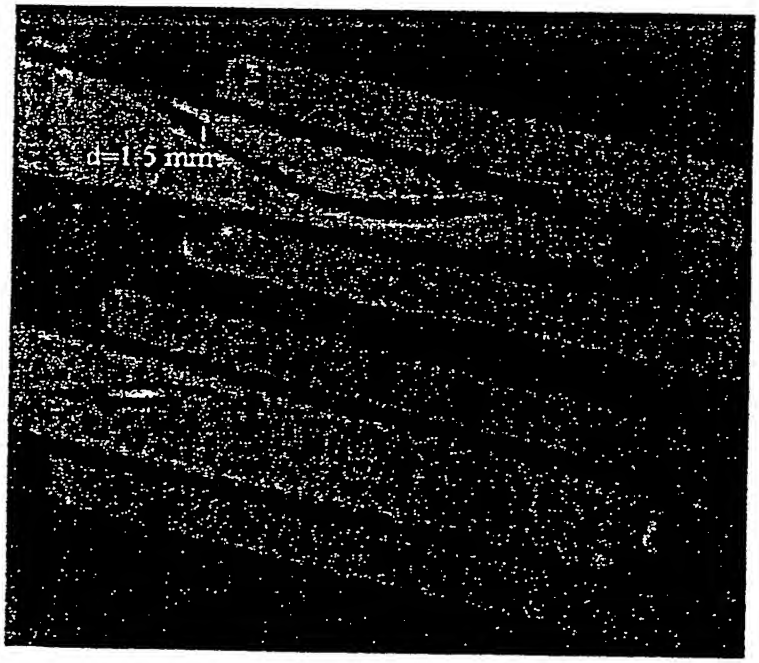
d=1.5 mm

FIG. 2

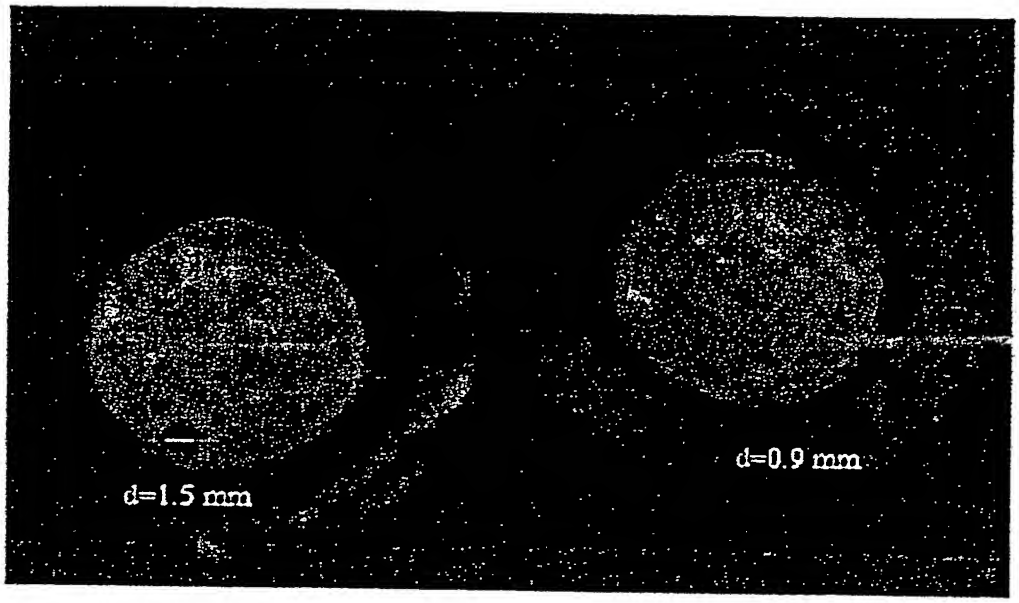

FIG. 3

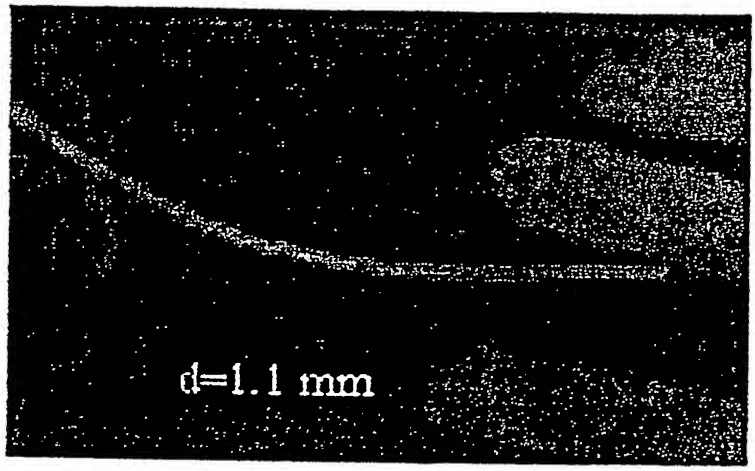

FIG. 4

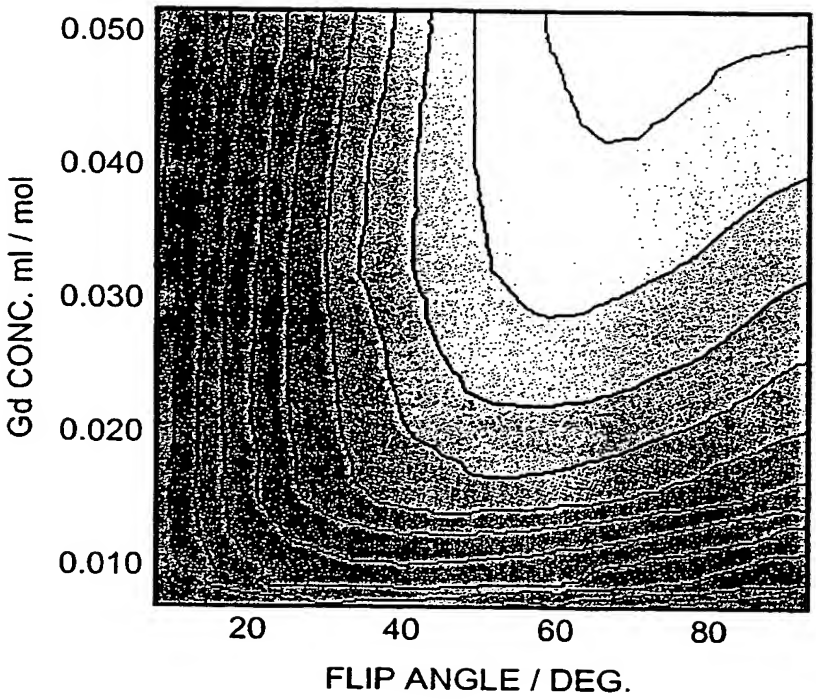
0.050
0.040
0.030
0.020
0.010
Gd CONC. ml / mol
20
40
60
80
FLIP ANGLE / DEG.

FIG. 5a

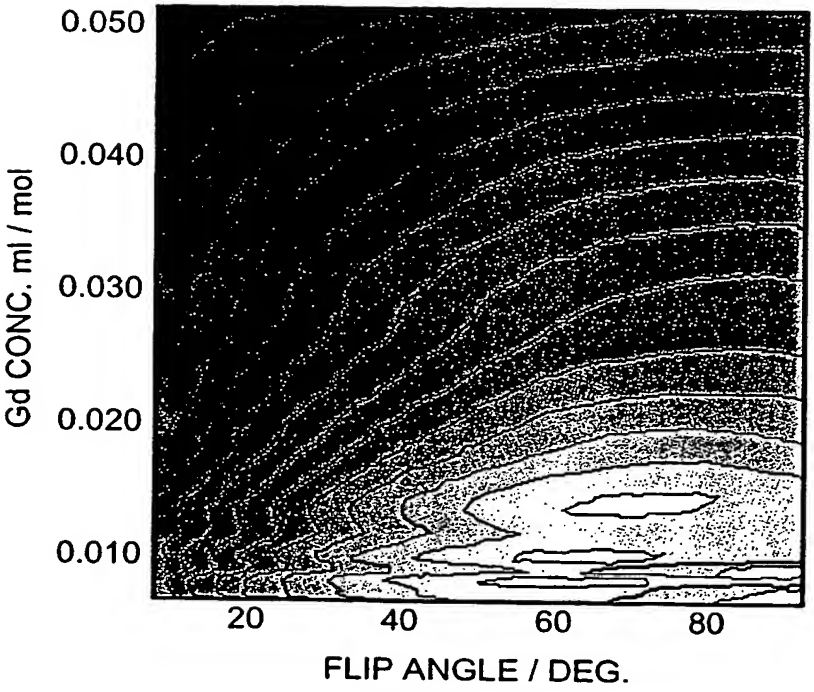
0.050
0.040
0.030
0.020
0.010
Gd CONC. ml / mol
20
40
60
80
FLIP ANGLE / DEG.

FIG. 5b

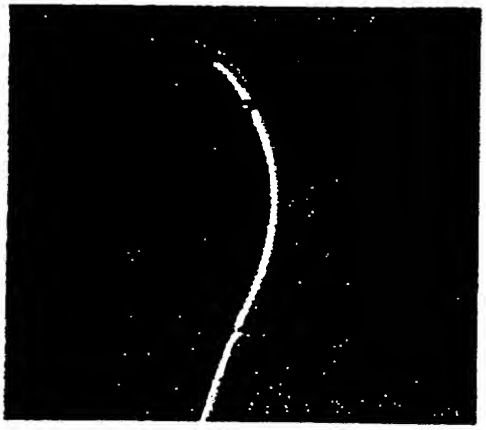

FIG. 6a

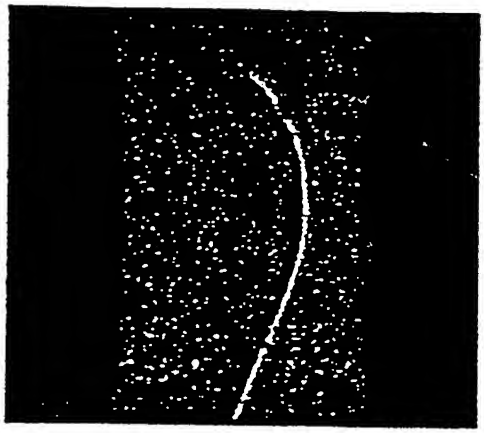

FIG. 6b

FIG. 7a

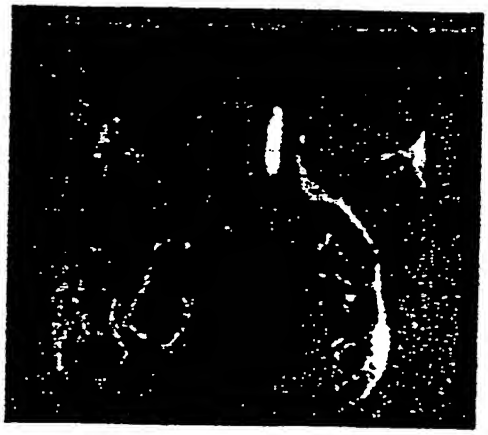

FIG. 7b

INTERNATIONAL SEARCH REPORT

Inte[redacted]al Application No
PCT/GB 00/01963

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01R33/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 609 153 A (CH.L. DUMOULIN, R.D. DARROW) 11 March 1997 (1997-03-11) column 2, line 31 - line 49 column 4, line 1 - line 52 claim 2	1-5, 10-12
X	US 5 479 925 A (CH.L. DUMOULIN, R.D. DARROW) 2 January 1996 (1996-01-02) column 2, line 49 - line 61 column 3, line 60 -column 4, line 35 column 5, line 26 - line 47	1-5, 10-12
A	EP 0 754 954 A (GEC-MARCONI LIMITED) 22 January 1997 (1997-01-22) column 1, line 27 -column 2, line 37	1,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2000	22/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Volmer, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PCT/GB 00/01963

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5609153 A	11-03-1997	DE 19626811 A	03-04-1997
		JP 9173317 A	08-07-1997
US 5479925 A	02-01-1996	DE 19521660 A	04-01-1996
		JP 8168473 A	02-07-1996
EP 754954 A	22-01-1997	DE 69608181 D	15-06-2000
		US 5735795 A	07-04-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
44.70151/002		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/01963	22/05/2000	21/05/1999
Applicant		
NYCOMED IMAGING AS		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01963

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01R33/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 609 153 A (CH.L. DUMOULIN, R.D. DARROW) 11 March 1997 (1997-03-11) column 2, line 31 - line 49 column 4, line 1 - line 52 claim 2 ---	1-5, 10-12
X	US 5 479 925 A (CH.L. DUMOULIN, R.D. DARROW) 2 January 1996 (1996-01-02) column 2, line 49 - line 61 column 3, line 60 -column 4, line 35 column 5, line 26 - line 47 ---	1-5, 10-12
A	EP 0 754 954 A (GEC-MARCONI LIMITED) 22 January 1997 (1997-01-22) column 1, line 27 -column 2, line 37 -----	1,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2000	22/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Volmer, W

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01963

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5609153 A	11-03-1997	DE 19626811 A	03-04-1997
		JP 9173317 A	08-07-1997
US 5479925 A	02-01-1996	DE 19521660 A	04-01-1996
		JP 8168473 A	02-07-1996
EP 754954 A	22-01-1997	DE 69608181 D	15-06-2000
		US 5735795 A	07-04-1998

PATENT COOPERATION TREATY

PCT

REC'D 31 AUG 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
44.70151/002		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01963	22/05/2000	21/05/1999
International Patent Classification (IPC) or national classification and IPC		
G01R33/28		
Applicant		
NYCOMED IMAGING AS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/12/2000	30.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Volmer, W Telephone No. +31 70 340 3516

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01963

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17 as originally filed

Claims, No.:

1-12 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-6, 10-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	7-9
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: US-A-5 609 153.

The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1 - 6 and 10 - 12 is not new in respect of the prior art as defined in the regulations [Rule 64(1) - (3) PCT]:

Document D1 discloses [cf. D1: abstract, col. 2, lines 31 - 49, col. 4, lines 1 - 52 and claim 2]:

- a method of interventional MRI, wherein an invasive device [a catheter] is inserted into the vasculature of a human body and an MR image of at least a part of said body containing said catheter [i.e. the vasculature surrounding the catheter] is generated, the method comprising the step of:

  - injecting an MR contrast agent directly into body of the patient [via the catheter] thereby to facilitate visualization of the catheter in the generated MR image.

    In D1, top of col. 4: once the fluid is polarized ... it is then injected through the catheter into the subject where it is imaged;

    therefore the polarized MR magnetic susceptibility contrast agent, injected into the patient's blood, hence a "blood pool contrast agent", facilitates visualization, as compared to the non-use of injected contrast agent, of at least part of the body containing the invasive device, i.e. visualization of the artery surrounding the inserted catheter, and visualization of the not-susceptibility-marked catheter through which it is injected and which catheter is surrounded by the injected contrast agent.]

Therefore, the subject-matter of claims 1, 2 and 10, 11 is not new.

Furthermore, D1 discloses [cf. D1: col. 4, lines 5 - 27] that the injected contrast agent has a T_1 value chosen such that in the image contrast is generated between the surrounding blood and the device of injection [the catheter]. Therefore, also the subject-matter of

claim 3 is not new.
Moreover, D1 discloses plural choices of fluids of magnetic susceptibility contrast agent [col. 4, 1) - 5)] which means that the device of injection is filled with a diamagnetic or a paramagnetic material. Therefore, also the subject-matter of claim 4 is not new.
As all magnetic susceptibility contrast agents, also the magnetic susceptibility contrast agent that is used in D1 enhances the T_1 or T_2^* relaxation properties of the blood relative to the device of injection. Therefore, also the subject-matter of claims 5 and 6 is not new.

Furthermore, D1 discloses the use of a "blood pool" MR contrast agent for the manufacture [via prepolarization] of a parenterally administrable MR contrast medium for use in a therapeutic method of MR imaging where a catheter is inserted into the vasculature of a human body and where an MR image of a part of said body containing said catheter is generated and where said contrast medium is administered into the vasculature of said body [via said catheter] whereby the visualization of said catheter in the generated MR image is facilitated. Therefore, also the subject-matter of claim 12 is not new.

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claims 7 - 9 does not involve an inventive step [Rule 65(1) and (2) PCT]:

Document D1 discloses [cf. the above cited passages] the use of a contrast enhancing agent enhancing the T_1 relaxation property of the blood relative to that of the inserted catheter.
It is well known in the art of MRI using contrast agents that an alternative to the method disclosed in D1 consists in the use of a well-known paramagnetic T_2^* enhancing contrast agent, which paramagnetic T_2^* enhancing contrast agents are constituted by magnetic iron oxide or of superparamagnetic iron oxide particles having on their surfaces degraded starch.
Obviously in the case of use of a T_2^* enhancing contrast agent, its effects have to be visualized by a T_2^*-weighted MRI sequence which results in that the inserted device appears bright relative to the surrounding blood.
Since it is straightforward for the person skilled in the art to replace the T_1 enhancing contrast agents together with the T_1-sequences that are used in the D1-method of visualizing an inserted device and the part of the body containing this device by this alternative, the subject-matter of claims 7 - 9 lacks an inventive step.

R Item VII

Certain defects in the international application

To meet the requirements of Rule 5.1(a)(ii) PCT, the document D1 should have been identified in the description and the relevant background art disclosed therein should have been briefly discussed.
Furthermore, the references of the prior art that is discussed on page 2, 2nd paragraph - page 3, 2nd paragraph should have been included in these passages.

To meet the requirements of Rule 6.3 (b) PCT, the independent claims should have been properly cast in the two part form, with those features / steps which in combination are part of the prior art [see document D1] being placed in the preamble and with those features / steps, which are not part of the prior art, being placed in the characterizing portion of the independent claims.

On page 5, 3rd paragraph and on page 6, 2nd paragraph reference is made to the prior art "which is incorporated herein by reference". It is not clear whether this expression is a reference to the background art or whether it is part of the disclosure of the invention [cf. the Guidelines C-II, 4.17]. Therefore, these expressions should have been deleted.

R It m VIII

Certain observations on the international application

The application does not meet the requirements of Article 6 PCT for the following reasons:

The following terms or expressions used in the claims are vague and indefinite and, as such, render the scope of the claims unclear; accordingly, the claims require amendment to remove these defects [Article 6 PCT]:

- to facilitate visualization of said device [claims 1 and 12: The point of reference, with respect to which visualization is facilitated, is not defined in the claims.];

- a blood pool contrast agent [claims 2, 8 and 12: The meaning of this expression is not defined in the claims. In order to meet the requirements of Article 6 PCT, i.e. defining the meaning of the expressions used in the claims without having to reference the description, it is suggested to use in the claims a definition as the definition on page 3, last paragraph.

Furthermore, it is suggested to include the specification of a "blood pool contrast agent" and the definition of this contrast agent in the subject-matter of the independent claim(s), in order to include all essential method steps of the invention in the subject-matter of the independent claim(s). Presumably, such amended claim(s) would meet the requirements of Article 33 PCT].

Claim 12 specifies:

- the use of a blood pool MR contrast agent for the manufacture of a parenterally administrable MR contrast medium for use in a method of surgery or therapy...

Since claim 12 does not specify any steps of manufacture, but specifies steps of a method of surgery or therapy, the category to which belongs the subject-matter of claim 12 is not clear.